REMARKS

Claims 34-43 are pending in the present application. The claims are related to a method of diagnosing neoplasms by using oncolytic viruses that are known to selectively replicate in neoplastic cells having a particular phenotype. For example, reovirus does not replicate in normal cells. However, reovirus selectively replicates in cells with an activated ras pathway and reovirus replication leads to the death of these cells. By using oncolytic viruses that are known to replicate in neoplastic cells with a particular phenotype, one can determine if a neoplastic cell has the phenotype for which the oncolytic virus is specific by determining if the oncolytic virus replicates in the neoplastic cell. Thus, the neoplasm can be diagnosed as comprising neoplastic cells with a particular phenotype. For example, a reovirus can be contacted with a neoplastic cell of an unknown phenotype. If the reovirus replicates in the neoplastic cell then the neoplastic cell has an activated Ras pathway. This is due to the fact that reovirus is known to only replicate in neoplastic cells with an activated Ras pathway. Claim 34 is amended herein to clarify these points rather than to narrow the scope of the claims. Support for these amendments can be found throughout the specification and at least at page 11, paragraph [0053]; page 13, paragraph [0061]; and page 14, paragraph [0066]. The Examiner is respectfully requested to enter the amendment. No new matter is added by entry of these amendments.

Interview Summary

On May 8, 2007, Tiffany Salmon discussed issues under 35 U.S.C. § 112, first paragraph with the Examiner. No final decision was reached.

35 U.S.C. § 112, First Paragraph, Enablement

Claims 34-43 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement for use of mixtures of oncolytic viruses.

Claim 34, as amended, defines a method of diagnosing a neoplasm in an animal by phenotype, comprising (a) providing a biological sample from the animal, wherein the sample comprises neoplastic cells with one or more unknown phenotypes; (b) providing at least two oncolytic viruses, wherein each oncolytic virus selectively replicates in neoplastic cells having a known phenotype selected from the group consisting of ras pathway activation, interferon-

resistance, p53-deficiency and Rb-deficiency; and wherein each of the at least two oncolytic viruses replicates in neoplastic cells having a known different phenotype; (c) contacting the neoplastic cells from the sample with each of the at least two oncolytic viruses under conditions which allow each oncolytic virus to selectively replicate in the neoplastic cells from the sample; (d) determining if each of the oncolytic viruses selectively replicates in the neoplastic cells from the sample; and (e) diagnosing a neoplasm in the animal as comprising cells of a known phenotype according to the ability of each of the oncolytic viruses to selectively replicate in the neoplastic cells from the sample.

Applicants point out that the wherein clauses in step (b) refer to the properties of the oncolytic viruses. Thus, reference to neoplastic cells in step (b) relates to the known ability of the oncolytic viruses to replicate in neoplastic cells of a known phenotype. The use of oncolytic viruses with known properties allows one to determine the phenotype of a neoplastic cell with a previously unknown phenotype. By using more than one oncolytic virus, one can determine multiple phenotypes of the neoplastic cells.

The Examiner states that Norman et al., *PNAS* 101(30):11099-11104 (2004) ("Norman"), demonstrates that reovirus can replicate in Ras-activated and Ral-activated cells and, therefore, if reovirus replicates in a cell, one could not determine whether the cell is Ras-activated or Ral-activated. Applicants respectfully point out that Ral is activated by Ras (see Norman on page 11099, at the paragraph spanning the left and right columns). Thus, Ral is a downstream signaling molecule in the *Ras pathway*. Thus, Ral activation is a result of Ras pathway activation. Norman states on page 11099, right column, third paragraph, that reovirus exploits the Ras/RalGEF/p38 pathway, i.e., the Ras pathway. Therefore, reovirus replicates in cells with an activated Ras pathway. "Activation of Ral" is subsumed in "activation of the Ras pathway."

The Examiner states that Table 2 of Smith and Chiocca, *Expert Opinion on Investigational Drugs* 9(2):311-27 (2000) ("Smith"), shows that oncolytic viruses are capable of selectively replicating in more than one pathway. Applicants respectfully disagree with the Examiner's characterization of Smith. Table 2 demonstrates that oncolytic viruses are capable of selectively replicating in cells with a specific phenotype. For example, Table 2 states that

E1B55kD adenoviruses replicate in p53 deficient cells and adenoviruses with a deletion in E1A replicate in Rb-deficient cells. Therefore, E1B55kD adenoviruses, for example, can be used to determine if a cell is p53 deficient. The cited portions of Smith and Norman fail to demonstrate that oncolytic viruses do not selectively replicate in a cell with a phenotype for which the oncolytic virus is specific.

Applicants note that the claims specify that the *oncolytic virus selectively replicates in neoplastic cells having a phenotype* selected from the group consisting of ras pathway activation, interferon-resistance, p53-deficiency and Rb-deficiency. The Examiner's argument is founded on an incorrect assumption, i.e., that the claims permit the use of viruses that are not selective. The claimed method comprises using oncolytic viruses that selectively replicate in neoplastic cells to allow diagnosing a neoplasm in the animal of a specific phenotype according to the ability of each of the oncolytic viruses to replicate in the neoplastic cells.

Further, the Examiner states that a person skilled in the art be unable to determine the phenotype of a neoplasm when using mixtures of two oncolytic viruses to differentiate the phenotype of a tumor, because both viruses will replicate. This aspect of the Examiner's argument incorrectly assumes that viral replication is only detected via cell death. However, the specification provides detection means that are specific to particular viruses and that can selectively detect the replication of each oncolytic virus if the method is conducted using a mixture of oncolytic viruses. Such detection means are described in the specification, for example, at least at page 7, paragraph [0037] and page 17, paragraph [0074]. Thus one of ordinary skill in the art can perform the claimed invention using mixtures of different oncolytic viruses. Consequently, in view of the teachings in the specification, the amount of experimentation needed to perform the claimed method is small and is not significantly greater than the amount of experimentation ordinarily performed in the art. Therefore, one of ordinary skill in the art can make or use the claimed method using the guidance provided in the application, coupled with information known in the art, without undue experimentation. Accordingly, Applicants submit that the specification fully enables the presently claimed method. Applicants respectfully request withdrawal of this rejection.

For the reasons set forth above, Applicants submit that the claims of this application are patentable. Reconsideration and withdrawal of the Examiner's objections and rejections are respectfully requested. Allowance of the claims of this application at an early date is earnestly solicited. Applicants also encourage the Examiner to call the undersigned at (404) 724-2760 in the event that this may facilitate prosecution of the present application.

It is believed that no fee is due at this time. However, please apply any charges or credits to deposit account 06-1050.

Respectfully submitted,

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